Monitoring and preserving diaphragmatic function in mechanical ventilation

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Purpose of review
This review summarizes the evidence on clinical outcomes related to diaphragm dysfunction, providing an overview on available monitoring tools and strategies for its prevention and treatment.

Recent findings
Long-term adverse functional outcomes in intensive care survivors are well documented, especially in patients with prolonged mechanical ventilation. Because diaphragm weakness is highly prevalent and strongly associated with weaning failure, a link between diaphragm weakness and adverse functional outcomes is probable. Mechanisms of critical illness-associated diaphragm weakness are complex and include ventilator-related myotrauma through various pathways (i.e. over-assistance, under-assistance, eccentric, expiratory). Given this potential clinical impact, research on preventive and therapeutic strategies is growing, including the development of ventilation strategies aiming at protecting both the lung and the diaphragm. Phrenic nerve stimulation and specific rehabilitation strategies also appear promising.

Summary
Diaphragm dysfunction is associated with adverse clinical outcomes in ventilated patients; therefore, their inspiratory effort and function should be monitored. Whenever possible, and without compromising lung protection, moderate inspiratory effort should be targeted. Phrenic nerve stimulation and specific rehabilitation strategies are promising to prevent and treat diaphragm dysfunction, but further evidence is needed before widespread implementation.

Keywords
diaphragm, diaphragm-protective ventilation, early rehabilitation, functional outcomes, mechanical ventilation

INTRODUCTION

Invasive mechanical ventilation (IMV) is not only life-saving but also associated with deleterious consequences. The clinical impact of ventilator-induced lung injury is well recognized. Recently, diaphragmatic myotrauma was described as another iatrogenic injury related to IMV with potential devastating consequences on long-term functional outcomes [1,2]. Evidence shows that inadequately applied ventilatory support drives diaphragmatic myotrauma rather than IMV *per se*, through low respiratory efforts (i.e. over-assistance myotrauma) and other potential mechanisms (i.e. under-assistance, eccentric contractions and expiratory myotrauma) [2–4]. This research has reinforced the importance of monitoring respiratory effort to implement both lung and diaphragm-protective ventilation strategies [5]. Diaphragmatic myotrauma is one facet of critical illness-associated diaphragmatic weakness (CIADW), a complex phenomenon resulting from numerous mechanisms of injury, such as systemic inflammation and drugs (e.g. neuromuscular blockers) [6]. CIADW has been shown to affect most mechanically ventilated patients with a prevalence higher than 60% [7,8].

As the primary inspiratory muscle, the diaphragms' force-generating capacity is a major determinant of successful ventilator liberation, as it is a key component of patients' capacity to overcome the load imposed to the respiratory system after extubation [9]. As a result, diaphragm weakness is associated with relevant patient-centered clinical outcomes, namely weaning failure leading to prolonged IMV tightly linked to long-term adverse

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KEY POINTS

- Diaphragm weakness is frequent in mechanically ventilated patients and probably contributes to prolonged mechanical ventilation, associated with adverse long term functional outcomes.
- Mechanisms of diaphragm weakness include diaphragmatic myotrauma closely linked to the magnitude of inspiratory effort during mechanical ventilation and resulting from inadequately applied ventilatory support.
- The first step to prevent myotrauma relies on monitoring inspiratory effort and function in ventilated patients; tools include esophageal manometry, noninvasive techniques using the ventilator (i.e. P0.1, Pocc and PMI), diaphragm ultrasound and electrical activity of the diaphragm.
- Whenever possible, and without compromising lung protection, moderate inspiratory effort should probably be targeted in most ventilated patients to prevent diaphragmatic myotrauma by personalizing ventilator settings and sedation.
- Emerging data on other preventive and therapeutic strategies including specific rehabilitation strategies and phrenic nerve stimulation are growing, however, clinical validation for widespread implementation is still needed.

functional outcomes in ICU survivors [4,7,8] and high mortality [8]. Thus, monitoring and preserving diaphragm function is of paramount importance. Additionally, despite accessory inspiratory and expiratory muscles playing an important role in supporting the diaphragm [10], their involvement in weaning failure has received far less attention.

In this review, we present an overview of mechanisms and outcomes of CIADW, focusing on the mechanisms of myotrauma, monitoring techniques of diaphragm activity and function, and preventive and therapeutic strategies for diaphragm dysfunction. A general overview of patients' trajectory during IMV including common clinical scenarios leading to diaphragm dysfunction, monitoring tools and suggested interventions for prevention and treatment are displayed in Fig. 1.

MECHANISMS OF DIAPHRAGMATIC MYOTRAUMA

Over-assistance myotrauma or unloading injury

Diaphragm inactivity achieved by anesthesia and suppression of respiratory drive is associated with a rapid and significant loss of diaphragmatic pressure-generating capacity in animal models [11] and with histological injury (i.e. disuse atrophy and ultrastructural muscle injury) in brain-dead organ donors [12]. Histological features are distinct from those of ICU-acquired weakness [13].

Deleterious consequences of excessive diaphragmatic unloading have been observed in observational studies in ICU patients [3,7]. Goligher *et al.* [3] found that 40% of patients experience a decrease in diaphragm thickness, a surrogate for atrophy, in the first 3 days of IMV. Atrophy was correlated with decreased respiratory effort, regardless of ventilation mode, and was less frequent when the magnitude of respiratory effort was similar to resting breathing in healthy subjects. Similarly, Hudson *et al.* [14] found that reported benefits of preserved diaphragm activity during assisted ventilation with triggered breaths on diaphragm function were no longer observed when high levels of support were applied, suggesting that the level of inspiratory effort, rather than the sole diaphragmatic contraction, is key in preserving diaphragm function.

Under-assistance myotrauma or load-induced injury

Goligher *et al.* [4] reported that around 25% of patients under IMV exhibit increased diaphragm thickness, associated with higher respiratory effort and longer duration of mechanical ventilation. This increase in diaphragm thickness possibly results from muscle edema and infiltrate secondary to injury in the context of excessive loading. Despite these mechanisms being speculative, the hypothesis is supported by animal studies and data in patients with chronic obstructive pulmonary disease, reporting diaphragm inflammatory infiltrates after breathing against an increased resistance [15,16].

Eccentric myotrauma

Strong eccentric muscle contractions are more injurious than concentric [17]. Diaphragm contractions can potentially be eccentric when occurring during exhalation, with cephalic displacement of the diaphragmatic dome and possible fiber lengthening. In a recent cohort study by Coiffard *et al.* [18▪], contractions occurring during mechanical exhalation were frequent (i.e. 13% of recorded hours early during IMV), especially during reverse triggering and premature cycling, and were associated with a progressive decline in diaphragm function. Risk of injury may however depend on the magnitude of the potentially eccentric respiratory effort as shown by an animal model where reverse triggering with

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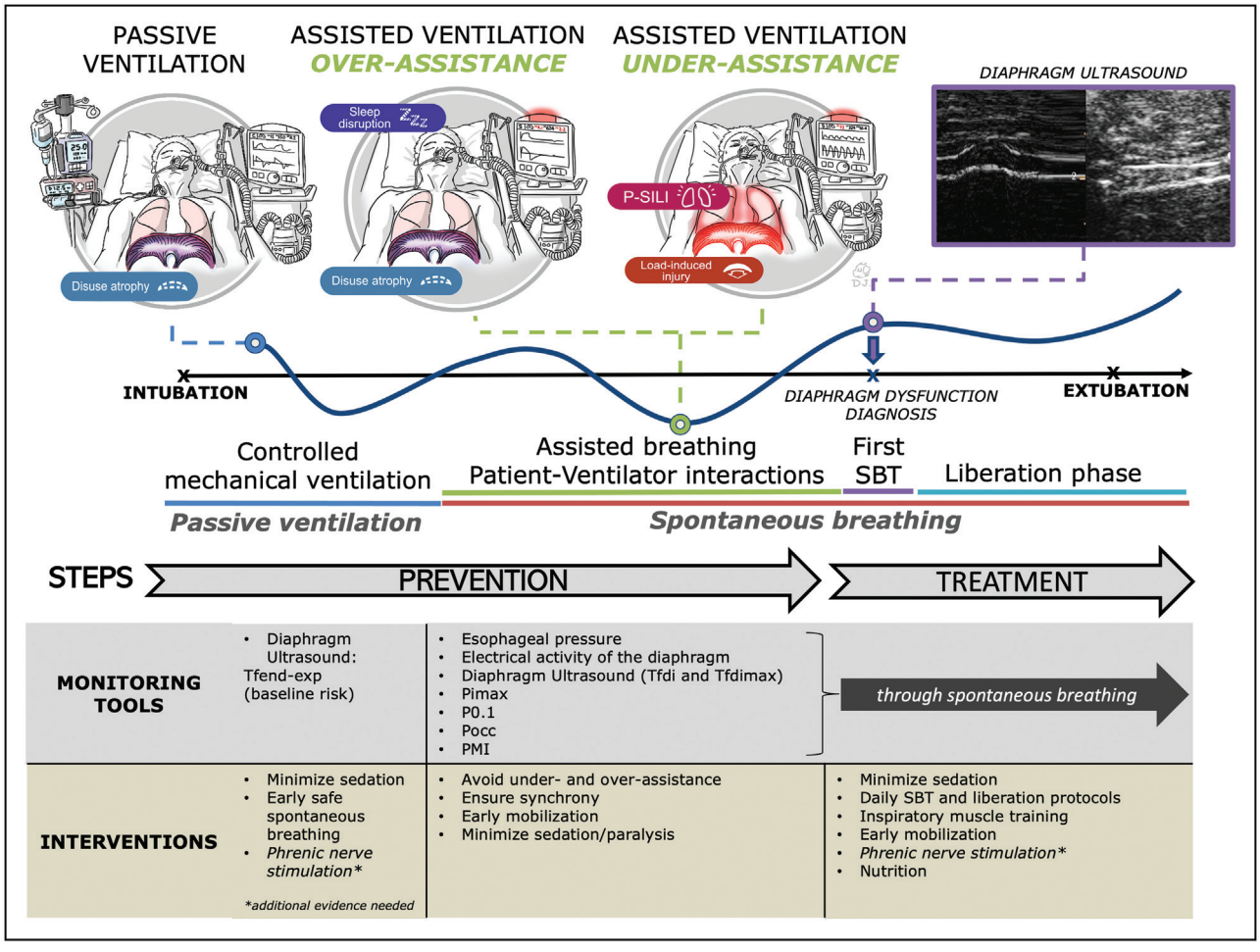

FIGURE 1. Monitoring, preventing and treating diaphragm dysfunction during mechanical ventilation. Most common patient trajectory during invasive mechanical ventilation is displayed from intubation to extubation with a visual representation of usual adverse consequences of common clinical scenarios in the top part including over-assistance and under-assistance. In the bottom of the figure, monitoring tools for diaphragm activity and function and suggested interventions for prevention and treatment are also displayed. P0.1, airway occlusion pressure; Pimax, maximum inspiratory pressure; Pocc, expiratory occlusion pressure; P-SILI, patient self-inflicted lung injury; SBT, spontaneous breathing trial; TFdi, diaphragm thickening fraction; TFdimax, maximum diaphragm thickening fraction; TFend-exp, end expiratory thickening fraction.

small magnitude of effort was associated with subsequent improvement in diaphragm function as compared to passive ventilation and strong reverse triggering events [19].

Expiratory myotrauma

Positive end-expiratory pressure (PEEP) induces caudal diaphragmatic displacement with fiber shortening and was associated with a rapid decrease in the number of sarcomeres available along muscle fibers [20]. Given the impairment of the length-ratio tension of the diaphragm, this 'longitudinal atrophy' could lead to diaphragm weakness, possibly clinically relevant when PEEP is abruptly reduced, such as during a spontaneous breathing trial (SBT). However, further studies are needed to confirm this clinically.

PREVALENCE AND CLINICAL OUTCOMES OF CRITICAL ILLNESS-ASSOCIATED DIAPHRAGMATIC WEAKNESS

Diaphragmatic dysfunction affects most ventilated patients during weaning

Reported prevalence of diaphragm dysfunction in ventilated patients is high but varies according to diagnostic technique, study population and timing of assessment, as summarized in Table 1.

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Table 1. Prevalence of later-onset diaphragm dysfunction

Study	Population	Diagnostic technique	Timing	Prevalence and mean measurements[a]	Significant association with outcomes
Watson *et al.* [21]	Medical and surgical ICU	Pdi,tw	Various duration of IMV	26/33 (79%) Mean Pdi,tw: 10 cmH_2O	
Laghi *et al.* [22]	Medical ICU	Pdi,tw	SBT Various duration of IMV	Pdi,tw in failure group: 9 ± 2 cmH_2O	
Kim *et al.* [23]	Medical ICU	US (excursion)	1st SBT	24/82 (29%)	Weaning failure
Hermans *et al.* [24]	Medical and surgical ICU, stable	Pdi,tw	Various duration of IMV	3/10 (30%) Mean Pdi,tw: 12 cmH_2O	IMV duration
DiNino *et al.* [25]	Medical ICU	US (TFdi)	1st SBT	16/63 (25%)	Weaning failure
Supinski *et al.* [26]	Medical ICU	Pdi,tw <10 cmH_2O	>7 days of IMV	Mean Pdi,tw: 8 cmH_2O	IMV duration Mortality
Lu *et al.* [27]	Prolonged weaning (>7 days)	US (TFdi)	>7 days of IMV	14/31 (34%)	IMV duration and ICU LOS
Jung *et al.* [7]	Medical ICU with ICU-AW	Pet,tw US (TFdi)	SBT IMV: 9 [6–15] days	Using Pet,tw: 32/40 (80%) Mean Pet,tw: 6.5 cmH_2O Using TFdi: 70%	
Dres *et al.* [8]	Medical ICU	Pet,tw US (TFdi and excursion)	1st SBT	48/76 (63%)	Weaning failure ICU and hospital mortality

ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; Pdi,tw, transdiaphragmatic pressure swing after standardized phrenic nerve stimulation through magnetic coils powered at their maximal output; Pet,tw, endotracheal twitch pressure; SBT, spontaneous breathing trial; TFdi, diaphragm thickening fraction; US, ultrasound.
[a]Range for Pdi,tw in healthy adult subjects is expected around 20–30 cmH_2O.

Weaning failure and mortality

Diaphragmatic dysfunction has been repeatedly reported as an accurate predictor of extubation failure [7,8]. Additionally, diaphragm weakness detected after several days of mechanical ventilation is associated with ICU and hospital mortality [8]. Evidence arising from a mediation analysis shows that diaphragm weakness is responsible for around 25% of the association between abnormal inspiratory effort and poor clinical outcomes. However, this does not definitely prove a causal relationship between CIADW and outcomes. Residual confounding may still remain, partly explaining the association [28]. Use of noninvasive respiratory support after extubation was not standardized in available studies and could highly influence the relationship between diaphragmatic function and weaning outcomes. Moreover, some patients are successfully weaned despite CIADW [7,8], which could suggest that it is the limited physiological reserve caused by diaphragmatic dysfunction that precipitates respiratory failure when coupled with a high respiratory load, rather than diaphragmatic dysfunction alone.

Long-term functional outcomes

Awareness of the devastating long-term functional impairments in ICU survivors has grown [29]. Despite little data being available on the direct long-term consequences of diaphragm dysfunction, one of the strongest predictors of very poor functional outcomes is prolonged IMV, closely linked to diaphragm dysfunction. In a large meta-analysis of over 30 studies including patients ventilated for at least 14 days, 80% did not return home at 1-year follow-up because of either death or severe disability [30]. In acute respiratory disease syndrome (ARDS) survivors, dyspnea is a frequent and debilitating symptom, and exercise tolerance remains impaired months or years after discharge, more closely associated with a neuromuscular dysfunction rather than pulmonary sequelae [31]. ICU-acquired limb weakness is a frequent and highly deleterious long-term impairment; however, there is limited overlap with diaphragm dysfunction. Data suggests that in ICU patients, diaphragm dysfunction occurs more frequently, and is more strongly correlated with prolonged weaning and long-term adverse outcomes [8].

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MONITORING OF DIAPHRAGM FUNCTION AND ACTIVITY

Historically, bedside assessment of diaphragm function and activity required costly and invasive techniques, mostly used for research in expert centers. Recently, the development of less invasive and cheaper surrogates (e.g. ultrasound assessment), or technological advances of classical techniques (e.g. esophageal pressure measurement) has made assessment more accessible. Main tools for monitoring of diaphragm function and activity are summarized in Table 2.

MANAGEMENT STRATEGIES TO PREVENT AND TREAT CRITICAL ILLNESS-ASSOCIATED DIAPHRAGM WEAKNESS

Maintaining adequate magnitude and timing of inspiratory effort

Evidence supporting the role of abnormal respiratory effort (i.e. too low or too high) in the development of diaphragmatic myotrauma has been summarized above. Even though randomized clinical trials (RCTs) are missing to confirm the impact of diaphragm-protective ventilation on clinical outcomes, modest inspiratory effort should probably be targeted in most patients. Ranges have been proposed by a consensus of experts of the Pleural Pressure Working Group (PLUG) and are displayed in Table 2 [5].

In moderate and severe acute hypoxemic respiratory failure, maintaining some respiratory effort without compromising lung protection can be challenging [32]. Experimental and clinical data support the existence of patient self-inflicted lung injury (P-SILI) defined as lung injury caused or aggravated by spontaneous breathing effort possibly mediated by the magnitude of effort, contributing to excessive global and regional lung stress and strain [32,33]. Airway pressures displayed on the ventilator do not consider distending pressures applied to the lungs by the respiratory muscles. Additionally, pendelluft phenomenon with regional overinflation can occur even when tidal volume delivered is within set limits [34]. Therefore, close monitoring of the magnitude of respiratory and total driving transpulmonary pressure is key to maintain sufficient diaphragmatic activity preventing disuse atrophy while avoiding both deleterious consequences of effort on the lung and diaphragm. These can be directly measured using esophageal manometry [35], or estimated by performing an end-expiratory occlusion to measure occlusion pressure (Pocc) and estimating muscular pressure and dynamic driving transpulmonary pressure (see Table 2 and details at *rtmaven.com*) [36].

Attention should also be paid to timing of inspiratory effort. Ensuring the ventilator cycles into expiration in synchrony with the end of inspiratory effort avoids dysynchronies, which might result in potentially eccentric diaphragm contractions. Dysynchrony detection can be achieved through direct flow and airway pressure waveform inspection [37], automated waveform analyses [38], or direct monitoring of diaphragm activity through esophageal manometry or electrical activity of the diaphragm.

Minimizing sedative and opioid use

Sedative drugs and opioids are other major modifiable factors potentially contributing to myotrauma through modifying magnitude and timing of breathing effort but could also play a role in CIADW through other, less understood mechanisms. Opioids primarily decrease respiratory rate and modify inspiratory time [39]. Propofol and benzodiazepines, both GABA agonists, decrease effort rather than rate [40]. Beneficial effects of lessening drive and effort in patients with moderate-to-severe lung injury to achieve a lung protective ventilation must be weighed against deleterious effects of inactivity on diaphragm function. Continuous sedation was shown to correlate with severity of diaphragmatic weakness and delayed resumption of diaphragmatic activity [41], as well as longer duration of weaning [42▪]. Therefore, continuous sedation should be used cautiously in patients with potentially excessive drive and effort and only after other possible contributors have been addressed (e.g. pain, acidosis, ventilator settings). Importantly, sedation use should be re-evaluated regularly. Moreover, because clinical sedation depth does not necessarily correlate with respiratory drive, drive should be monitored directly [e.g. by measuring airway occlusion pressure (P0.1)] when sedation is used to modulate it [43].

Phrenic nerve stimulation

Phrenic nerve stimulation (PNS) to elicit diaphragm contraction is used in patients with cervical cord injury and as the gold-standard diagnostic tool to assess diaphragm function in ICU patients [21]. Therapeutic applications of temporary PNS in ventilated ICU patients are currently under investigation. As a therapeutic strategy, i.e. muscle training to shorten weaning duration in patients with diaphragm dysfunction, PNS through temporary intravenous pacing via left internal jugular or subclavian access was shown to be safe, feasible and associated with increased diaphragm force [44]. However, in an RCT by Dres *et al.* [45], this increase in diaphragm force did not translate into a significant decrease in weaning failure or IMV duration.

As a preventive strategy, that is, maintenance of diaphragm activity in the early stages of IMV,

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Table 2. Techniques for monitoring of diaphragm activity and function

Technique	Measurement	Significance	Strengths and limits	Reference values
Diaphragm pressure-generating capacity [46]	Pdi,max	- Reference method for evaluation of diaphragm function in cooperative patients.	- Invasive: gastric and esophageal balloon insertion - Patient cooperation	- HS 100–150 cmH_2O in healthy subjects - Diaphragm weakness: $<60\ cmH_2O$
Reference method diaphragm function assessment	Pdi,tw	- Reference method for evaluation of diaphragm function in ICU.	- Invasive: gastric and esophageal balloon insertion - Standardized measurement, independent of patient's cooperation	- Diaphragm weakness: $<-10\ cmH_2O$
	Pet,tw	- Surrogate of Pdi,tw measured at tip of endotracheal tube.	- Idem Pdi,tw. - Does not require gastric or esophageal balloons. - Includes extra-diaphragm respiratory muscles.	- Diaphragm weakness: $<-11\ cmH_2O$
End-expiratory airway occlusion	P0.1 [47]	- Drop in airway pressure during the first 100 ms of occluded breath. - Surrogate for respiratory drive.	- Simple and automated measure available on most ventilators. - Not influenced by mechanics or muscle dysfunction. - Can lead to overestimation of effort in case of muscle weakness.	- Low in ICU if $<1.3\ cmH_2O$
	Pocc [36]	- Magnitude of negative deflection in airway pressure during an occluded breath. - Pmus (pressure generated by respiratory muscles during inspiration) = $-0.75 \times$ Pocc - $\Delta P_{L,dyn}$ (dynamic transpulmonary pressure) = $P_{peak} - PEEP = 2/3 \times$ Pocc	- Simple bedside measurement of respiratory effort (Pmus) and transpulmonary pressure applied to the lung ($\Delta P_{L,dyn}$). - Good for detection of high drive, not validated for low drive.	- High in ICU $>10–15\ cmH_2O$
Ultrasound [48] Right hemi-diaphragm via subcostal (excursion) and intercostal – 8th to 10th intercostal spaces mid- anterior axillary line- (Tfdi) approach	Excursion - Inspiratory caudal diaphragm displacement. - Only without inspiratory assistance (i.e. TP or CPAP). - During tidal breathing (activity) or maximal effort (function).	- Association with weaning outcomes (i.e. higher excursion associated with weaning success) - Poor correlation with markers of pressure-generating capacity	- Easy bedside measurement. - High inter-operator variability. - Not continuous.	- HS: women >3.6 cm and men >4.7 cm. - Diaphragm weakness: <1 cm associated with weaning failure
	Thickening fraction (TFdi) TFdi = (Tei – Tee)/Tee (%) - During tidal breathing (activity) or maximal effort (function), i.e. Tfdimax.	- Variable correlation between TFdi and pressure-generating capacity. - Correlated with weaning success (meta-analysis).	- Easy bedside measurement. - High inter-observer variability. - Not continuous.	- Diaphragm weakness: $<29\%$ diaphragm dysfunction $<20–25\%$ is associated with weaning failure
	Diaphragm thickness at end-expiration (Tee) [3,4].	- Poorly correlated with pressure-generating capacity - Decreased thickness, surrogate for atrophy, associated with lower effort - Increased thickness, associated with excessive effort - Both associated with worse weaning outcomes.	- Easy to measure - High inter-observer variability. - Measure of structure, not activity or function.	- 10% increase and 10% decrease in Tee within first 3 days of MV are associated with worsened clinical outcomes

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Table 2 (*Continued*)

Technique	Measurement	Significance	Strengths and limits	Reference values
Electrical activity of the diaphragm [49] Temporal and spatial summation of muscle action potentials	EAdi – nasogastric catheter (crural diaphragm) - Diaphragm electrical activity through multiarray esophageal electrodes. - During tidal breathing (EAdipeak) or maximal effort (EAdimax)	- Correlates well with pressure-generating capacity	- Special nasogastric feeding tube - Not available on all ventilators - Expensive	- No absolute reference values available
	Surface EMG Idem through surface electrodes	- Correlates well with EAdi	- Continuous and noninvasive - Electrocardiogram interference and crosstalk from neighboring muscles	- No reference values available
	Neuromechanical coupling - Derived from EAdi measuring transformation of electrical activity pressure generating capacity.	- ΔPdi/ΔEAdi. - ΔPaw/ΔEAdi during an end-expiratory hold. - Continuous estimation of inspiratory effort by multiplying ratio × EAdipeak.	- Require end-expiratory hold (ΔPaw/ΔEAdi). - Continuous. - Surrogate for diaphragm function without patient's cooperation.	- No reference values

CPAP, continuous positive airway pressure; EAdi, electrical activity of the diaphragm; EAdi max, maximum electrical activity of the diaphragm; EAdi peak, peak electrical activity of the diaphragm; EMG, electromyography; HS, healthy subjects; IMV, invasive mechanical ventilation; Paw, airway pressure; Pdi, trans diaphragmatic pressure, defined as difference between pleural pressure (measured through esophageal pressure) and abdominal pressure (measured through gastric pressure); Pdi,tw, transdiaphragmatic pressure swing after standardized phrenic nerve stimulation through magnetic coils powered at their maximal output; Pdi,max, maximal trans diaphragmatic swing; PEEP, positive end-expiratory pressure; Pet,tw, endotracheal twitch pressure; P_{peak}, peak airway pressure during inspiration; Tee, end-expiratory diaphragm thickness; Tei, end-inspiratory diaphragm thickness; TP, T-piece; Tfdi diaphragm thickenning fraction.

continuous temporary PNS was recently shown to be feasible and to effectively maintain diaphragm activity in the early results of a phase 1 RCT [50▪]. More data for therapeutic and preventive clinical implications of PNS is warranted. Noninvasive percutaneous techniques through magnetic stimulation were recently developed and shown to be feasible, but data on their clinical impact are also lacking [51].

Additional rehabilitation strategies

Extra-diaphragmatic and expiratory muscle involvement

Like the diaphragm, the extra-diaphragmatic inspiratory muscles, responsible for supporting the diaphragm to maintain adequate ventilation [10] and expiratory respiratory muscles, responsible for cough, secretion clearance, and inspiratory flow generation [52], may also display some degree of injury during mechanical ventilation [53]. Patients who fail SBTs have increased expiratory muscle recruitment [52] and lower maximal expiratory pressures (MEP) [54], although data on specific association of these muscles' dysfunction with outcomes is lacking.

Inspiratory muscle training

Inspiratory muscle training (IMT) is a well tolerated and feasible intervention for ventilated patients, used to increase the activity, strength and endurance of the inspiratory and expiratory muscles [55]. While ideal parameters (frequency, intensity and timing) of IMT remain unclear, threshold loading, a technique in which patients overcome a preset pressure threshold using the ventilator trigger or an external device, may be associated with increased muscle strength, measured by maximal inspiratory and expiratory pressures, when compared to other techniques such as flow resistance loading, in which patient generates flow against a constant resistive load [56], general physical therapy, and diaphragmatic breathing exercises [55]. However, IMT sometimes requires active patient participation for generating effort, anticipating brief ventilator disconnection, and tolerating temporary respiratory discomfort, which cannot be obtained early in many ICU patients due to sedation, cognitive impairment and/or severity of medical condition [56]. This warrants consideration for earlier passive rehabilitative approaches aimed at mitigating respiratory muscle weakness.

Surface electrical muscle stimulation

Electrical muscle stimulation (EMS) is a noninvasive, passive therapeutic modality used to prevent muscle atrophy by stimulating motor nerves to cause muscle contractions [57]. In spinal cord injury, EMS has been used to improve respiratory function [58]; however, the same has not been found for general ICU populations. Although most ICU studies focus on limb muscle function [59], several RCTs including respiratory outcomes have shown that abdominal electrical stimulation may

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help preventing respiratory muscle atrophy and shorten ICU stay [60]. Others have found that, even when targeting nonrespiratory muscles, EMS may reduce mechanical ventilation duration [61] and in combination with physical therapy, could increase extubation success [62]. However, when evaluating surface diaphragmatic stimulation, a technically challenging technique, studies have found no significant results [59]. Further large-scale trials are needed to validate the effectiveness of surface electrical stimulation for respiratory muscle strengthening.

Early mobilization

Evidence suggests that physical rehabilitation initiated within the first days of ICU admission may mitigate deleterious consequences of immobility by increasing muscle strength, reducing IMV duration and improving functional outcomes [63]. Recent data suggests that early mobilization at maximum intensity could, however, lead to more adverse events without improving long-term outcomes [64], probably driven by specific harm in certain subgroups, such as diabetic patients [65▪]. In contrast, evidence suggests that early lower dose, higher frequency interventions are better tolerated and may improve ventilator-related outcomes [66,67].

Less evidence focusing on benefits of early mobilization on diaphragm function is available with only one study reporting improved diaphragm thickening and reduced IMV duration [68]. Despite significant advances seen over the last years, more research is needed to understand how to tailor early mobilization to specific patients, when, at what dose and how frequently and to investigate specific beneficial diaphragm-related outcomes.

CONCLUSION

Critical illness-associated diaphragm weakness including diaphragmatic myotrauma has emerged as a frequent and plausible cause of prolonged mechanical ventilation in ICU patients, strongly associated with mortality and devastating functional consequences in ICU survivors. Close monitoring of inspiratory effort and sedation minimization appears pivotal in balancing lung and diaphragm-protective ventilation and preventing diaphragmatic myotrauma. PNS and rehabilitation strategies appear as promising strategies for prevention and treatment of diaphragmatic myotrauma, but further RCTs are warranted.

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Conflicts of interest

I.T. reports personal fees from Medtronic, Getinge and MbMED SA, Argentina outside of the submitted work.

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- ▪ of special interest
- ▪▪ of outstanding interest

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